UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,046	11/20/2001	Frederic J. de Sauvage	P1405R1C1	1433

9157 7590 07/15/2008

GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO, CA 94080

EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
07/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/990,046	DE SAUVAGE ET AL.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29,30,36-40,46-49 and 52-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,30,36-40,46-49 and 52-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 3/21/08 has been entered.

Status of Application, Amendments and/or Claims

On 3/21/08, Applicants filed an Amendment After Final. As noted above, this amendment has been entered in view of the Request for Continued Examination (RCE) filed on 4/29/08. The 3/21/08 amendment states that there are no claim amendments, and includes a claim listing with each pending claim listed as "Previously Presented".

Claims 29, 30, 36-40, 46-49 and 52-54 are pending in the application.

Withdrawn Objections and/or Rejections

The rejection of claims 29, 30, 36-40, 46-49, 52-54 under 35 U.S.C § 112, second paragraph, at pg 2-5 of the 10/30/07 Office Action for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is *withdrawn* on further consideration by the Examiner.

On further consideration by the Examiner, the term "specifically binds" as used in the claims is broad but not indefinite. It is noted that the Examiner maintains that the term "specifically binds" as used in the claims broadly encompasses an antibody that binds to an identical epitope that is found within two otherwise different proteins. Such an antibody specifically binds to these two proteins and is non-specific for other proteins lacking this epitope. All of Applicants' arguments with respect to this interpretation have been fully considered but are not persuasive for the reasons set forth below.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 29, 30, 36-40, 46-49 and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Motoyama et al. (18 February 1998. Nat Genet. 18(2): 104-6) in view of Tso et al (U.S. Patent No. 5,932,448, published 3 August 1999, and filed 11/29/1991). This rejection was maintained at pg 5-7 of the 10/30/07 Office Action.

For purposes of clarity, the rejection as set forth previously is reiterated, and then Applicant's arguments are addressed.

Claims 29, 30, 39, 40 and 49 each encompass a monoclonal antibody that "specifically binds" to a patched-2 polypeptide of instant SEQ ID NO: 2, or variants of SEQ ID NO: 2 that are at least 95% identical and bind to a *hedgehog* or *Smoothened* polypeptide. The remaining claims depend from claims 29, 39 or 49 and limit the antibodies to those that are humanized (claims 36, 46 and 52), bispecific (claims 37, 47 and 53), or heteroconjugated (claims 38, 48 and 54).

Motoyama teaches the mouse gene Ptch2 that encodes the polypeptide patched-2. The sequence of the mouse patched-2 polypeptide is 89.3% similar to instant SEQ ID NO: 2 (which is the human patched-2 polypeptide). An alignment of the two sequences was attached to the 7/12/05 Office Action as Sequence Alignment #1. Motoyama does not teach an antibody to the mouse patched-2 polypeptide.

Tso teaches general methods for producing bispecific antibodies (col 1, line 62-67); monoclonal antibodies for use in production of bispecific antibodies (col 7, line 19); humanized antibodies for use in bispecific antibodies (col 2, lines 46-47); and chemical cross-linking of two antibodies to produce a bispecific antibody (col 1, lines 34-35). The instant specification defines heteroconjugated antibodies as “antibodies composed of

two covalently joined antibodies (pg 26). Thus, the bispecific antibody taught by Tso meets the definition of a "heteroconjugated" antibody as defined by the specification.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to make antibodies as taught by Tso to the mouse patched-2 polypeptide taught by Motoyama. The person of ordinary skill in the art would be motivated to do so because Tso teaches that the antibodies have general uses applicable for use with any protein, such as cross-linking a horseradish peroxidase for purposes of detection (see col 11, lines 52-55). The person of ordinary skill in the art would have expected success because Motoyama teaches the sequence of mouse patched-2 polypeptide, and Tso teaches the methods necessary to produce antibodies to any protein sequence.

Such antibodies are encompassed by the instant claims for the following reasons. Due to the high degree of similarity between the two sequences, including numerous regions of 20 or more amino acids with 100% identity between the sequences, one of skill in the art would reasonably predict that numerous monoclonal antibodies (including bispecific, humanized, or heteroconjugated antibodies) made to mouse patched-2 polypeptide as taught by Motoyama would specifically bind to the human patched-2 polypeptide of instant SEQ ID NO: 2. The regions of exact identity contain epitopes that would generate monoclonal antibodies that would bind to either protein, particularly if the proteins are denatured and presented in linear form. The term "specifically binds" is not defined in the specification as excluding antibodies that bind to the same epitope in other proteins (e.g., mouse patched-2); and therefore broadly encompasses antibodies that bind to the same epitope in two different sequences. Therefore, as many of the monoclonal antibodies to mouse patched-2 would also bind to instant SEQ ID NO: 2, the teachings of Motoyama in view of Tso render obvious the antibodies encompassed instant claims.

Applicants' arguments (3/21/08; pg 4-7) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

Applicants argue that the Examiner has erroneously interpreted the term "specifically bind" and if interpreted correctly in view of the "scope and the content of the prior art", the teachings of Motoyama et al in view of Tso et al would not fall within the scope of the claims (pg 6). Applicants refer to arguments presented in response to the rejection under 35 U.S.C. 112, 2nd paragraph (now withdrawn). These arguments include the following. Applicants argue (pg 4) that when an antibody binds to the same epitope in two different proteins, this is known in the art as a cross-reaction and not specific-binding. In support of this argument, Applicants submit page 6.3 of the text Immunology by Roitt et al (1985) and argue that this page clearly defines the two terms. Applicants further argue (pg 5) that Van Regenmortel (1998) was published after the Applicants' priority date and is an inappropriate reference to define a term of art at the time of filing. Applicants further argue (pg 5) that "Van Regenmortel's discussion of specificity represents a departure or new concept in the use of the term "specificity" than the accepted term in general use in the field of immunology at the time of filing". Applicants further argue that Figure 1 of Van Regenmortel "shows that reactivity of an antibody raised against Antigen 1 with the same epitope as Antigen 2 is referred to as cross-reactivity".

Applicants' arguments have been fully considered but are not found persuasive. In the quoted section of Roitt (from page 6.3) the concept of "specificity" is discussed as a term of degree; i.e. a "high level of specificity". Thus, "specificity" ranges from a "low level of specificity" to a "high level of specificity". In the instant claims and specification the degree of the term "specifically binds" is not defined, and thus encompasses both "low levels of specificity" and "high levels of specificity". Thus, the recitation of "specifically binds" in the instant claims is not limited to a definition of a "high level of specificity" as used by Roitt.

Furthermore, Roitt describes a "high level of specificity" by the relationship of an antibody to each of two different antigens; i.e. when "the binding sites of antibodies directed against determinants on one antigen are not complementary to determinants of another antigen". In contrast, the instant claims use the term "specifically binds" in relation to a single genus of antigens (polypeptides that have at least 95% to SEQ ID

NO: 2). Roitt also teaches that "[t]he specificity and cross-reactivity expressed by an antiserum are properties which result from the antibody molecules within the serum" which indicates that an antiserum can have both qualities of specificity and cross-reactivity (i.e., they are not mutually exclusive). In Roitt's example in Figure 6.8 on page 6.3, Roitt describes an antibody that is "reacts specifically with the sulphonate group (which has a tetrahedral structure) in the meta position but will give a cross-reaction (though weaker) with sulphonate in the ortho position". Thus, Roitt provides an example of an antibody that specifically binds a particular epitope but also experiences cross-reactivity. There is no teaching in Roitt that precludes the term "specifically binds" as used in the instant claims from encompassing an antibody that binds to an identical epitope that is found within two otherwise different proteins (e.g., instant SEQ ID NO: 2 and the mouse Ptch2 polypeptide taught by Motoyama). Such an antibody "specifically binds" to this epitope but not to other epitopes (and thus not to other proteins lacking this epitope). Thus antibodies that bind to shared epitopes on SEQ ID NO: 2 and mouse Ptch2 "specifically bind" to these two proteins and but are non-specific for other proteins.

With respect to Applicants' argument concerning the Van Regenmortel (1998), it is true that Van Regenmortel was published July 1st, 1998, which is several months after the earliest claimed priority date (provisional application 60/081884, filed 4/15/1998). However, the publication date of Van Regenmortel does not make it an inappropriate reference to define a term of art at the time of said priority date. As quoted by Applicants themselves on page 5 of the response, Van Regenmortel states, "[t]he purpose of this paper … is to discuss the notion of specificity itself and the way this concept has been used in the field of immunology". Therefore, Van Regenmortel states that the purpose of article is to review the state of the art prior to the publication date. In the section following this quotation (titled "What is specificity?"), Van Regenmortel cites papers published from 1978 through 1995, and elsewhere Van Regenmortel cites papers published from 1957 through 1997. Furthermore, there is nothing in Van Regenmortel that leads to the conclusion that the state of the art has changed between April and July 1998. Therefore, in contrast to Applicants' argument, the teachings of Van

Regenmortel are highly appropriate to the rejection. Furthermore, Van Regenmortel's teachings do not represent a departure from the accepted use of the term "specificity" in the prior art. In contrast, and as discussed in the previous Office Action, Van Regenmortel teaches that the prior art itself does not provide a strict definition of the term "specificity" in relationship to antibody binding.

Applicants' arguments with respect to Figure 1 of Van Regenmortel are not persuasive because, as in the teachings of Roitt, the terms "cross-reactive" and "specifically binds" are not mutually exclusive. On page 42, Van Regenmortel discusses cross-reactivity, stating that "One type of cross-reactivity, more properly called shared reactivity, arises when a particular antibody recognizes the same epitope in two different multideterminant proteins. This corresponds to the absolute specificity Ehrlich had in mind since the antibody then reacts in an identical fashion with the same complementary epitope present in the two antigens". This is illustrated in Figure 1 with respect to the "anti a" antibody, which binds to an identical epitope in "Antigen 1" and "Antigen 2". Thus according to Van Regenmortel's teachings, the "anti a" antibody is both cross-reactive (because it binds to both antigens) but also specific for the shared epitope and no other epitopes.

It is maintained that Van Regenmortel teaches that “[a]lthough the concept of specificity is widely used in biology, few authors have attempted to define it” (pg 37 of Van Regenmortel. 1998. Journal of Immunological Methods. 216: 37-48). Van Regenmortel (1998) further teaches, “[a]ntibody specificity is a ternary relational property which refers to the antibody’s capacity to discriminate between two or more epitopes” (see Abstract). This supports that “specifically binds” can refer to the ability of an antibody to distinguish two different epitopes rather than two different antigens.

In summary, the relevant art, including both Roitt and Van Regenmortel, supports that the term “specifically binds” as used in the instant claims and specification encompasses an antibody that binds to the same epitope in two different protein sequences. Thus, it is maintained that antibodies produced according to Tso to the mouse patched protein taught by Motoyama would specifically bind to instant SEQ ID NO: 2, in view of the many common sequences found in each protein.

Conclusion

No claims are allowable.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646